May 8, 2003

F.J. Sonny Maher
Panel Manager, HQPD
The American Chemistry Council
The Hydroquinone Precursors and Derivatives (HQPD)
Panel HQMME Task Force
1300 Wilson Boulevard
Arlington, VA 22209

Dear Mr. Maher:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for 4-Hydroxyanisole posted on the ChemRTK HPV Challenge Program Web site on January 21, 2003. I commend The American Chemistry Council's Hydroquinone Precursors and Derivatives Panel HQMME Task Force for their commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that The American Chemistry Council's Hydroquinone Precursors and Derivatives Panel HQMME Task Force advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: C. Auer
A. Abramson
W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
4-Hydroxyanisole

Summary of EPA Comments

The sponsor, the Hydroquinone Precursors and Derivatives Panel (HQPD) Hydroquinone Monomethyl Ether (HQMME) Task Force of the American Chemistry Council, submitted a test plan and robust summaries to EPA for 4-hydroxyanisole (CAS No. 150-76-5) dated December 20, 2002. EPA posted the submission on the ChemRTK HPV Challenge Web site on January 21, 2003.

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical Properties and Environmental Fate. Adequate data are available for all endpoints except for vapor pressure. The submitter needs to provide measured data for vapor pressure.

2. Health Effects. (a) Adequate data are available for the acute and repeated-dose toxicity endpoints. The submitter needs to address deficiencies in the acute toxicity study robust summary. (b) Data are inadequate for gene mutations. (c) EPA reserves judgement on the adequacy of data for the chromosomal aberrations and reproduction/developmental toxicity endpoints pending submission of information on bioavailablity of this chemical, since available data are via the dermal route and oral/inhalation are the major routes of exposure for this chemical.

3. Ecological Effects. (a) Submitted data for fish acute toxicity are adequate; however, the submitter needs to provide missing study details in the robust summary. (b) EPA reserves judgement on the adequacy of data for invertebrate toxicity pending submission of additional information. (c) For algae, the submitter needs to conduct a test according to OECD TG 201.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the 4-hydroxyanisole Challenge Submission

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

Available data for melting point, boiling point, water solubility, and partition coefficient endpoints are adequate for the purposes of the HPV Challenge Program.

Vapor Pressure. The submitter states that measurement of vapor pressure of 4-hydroxyanisole is not applicable since it is a solid. However, EPA believes that the submitter needs to provide the measured vapor pressure value because the EPIWIN estimated vapor pressure is 8.3×10^{-3} mm Hg at 25°C (1.103 Pa) and OECD TG 104 states that measured data are required for addressing this endpoint when the estimated vapor pressure is greater than the cutoff value of 7.5×10^{-8} mm Hg (1×10^{-5} Pa) at 25°C.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

Available data for these endpoints are adequate for the purposes of the HPV Challenge Program.
Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

Adequate data are available for the acute and repeated-dose toxicity endpoints for the purposes of the HPV Challenge Program. The submitter needs to address deficiencies in the acute toxicity study robust summary.

Genetic Toxicity. Gene Mutations: The data for gene mutations were not adequate because one study was a spot test and provided only limited information and in the other study, only two strains were tested.

EPA notes that the micronucleus, cancer, two-generation reproductive, and developmental toxicity tests were performed in 1997 and submitted to the FDA as part of a New Drug Application (NDA). All these studies were conducted using the dermal route of exposure because the applicant was seeking approval for a minor use of 4-hydroxyanisole in a topical dermatological product (by prescription only) to lighten skin. EPA questions whether this route of test substance administration was dermally bioavailable to produce any systemic toxicity and was appropriate for these endpoints for the purposes of the HPV Challenge Program. Most importantly, the submitter stated that the inhalation route is of most concern in the occupational environment. Therefore, EPA reserves judgment on the adequacy of these data and requests that the submitter either provide information on relative bioavailability of the oral/inhalation route versus the dermal route (for which they have the most data), provide adequate analog data, or conduct appropriate testing.

Ecological Effects (fish, invertebrates, and algae).

Fish. The data are adequate for the purposes of the HPV Challenge Program; however, the submitter needs to provide missing study details in the robust summary.

Invertebrates. EPA reserves judgement on the adequacy of the data for this endpoint until missing study details are provided.

Algae. EPA believes that this endpoint has not been adequately addressed because the submitted study on *Microcystis aeruginosa* (cyanobacteria) is not the appropriate species for algal toxicity testing and the exposure period is too short (24-hours). The study on *Scenedemus quadrcauda* (algae) is inadequate because the required study details are not available, the exposure period (10-days) is too long, and the data are insufficient for derivation of an EC_{50} value. Therefore, EPA recommends that the submitter conduct an algal test according to OECD TG 201.

Specific Comments on the Robust Summaries

Environmental Fate

Photodegradation. The submitter needs to clarify whether the summarized test (Ref. 5) is for "INDIRECT PHOTOLYSIS" as stated in the robust summary. The summary methodology suggests that the study was for "DIRECT PHOTOLYSIS."

Fugacity. The submitter needs to provide input parameters in the level III modeling summary.

Health Effects.

Acute Toxicity. Omissions include: the gavage vehicle, length of the observation period, the strain and sex of rat, the exact doses administered on a mg/kg basis, information on target organs, and the method for estimating the LD_{50}.

Ecological Effects

Fish. Information missing includes GLP compliance, the number of fish tested, concentrations tested, mortality/effects seen at each concentration, water quality characteristics, and statistical methods used.

Invertebrates. Information missing includes GLP compliance, test methods/guidelines used, the number of daphnids tested, test substance purity, concentrations tested, mortality/effects seen at each concentration, water quality characteristics, statistical methods used, and whether the reported 48-hour EC_{50} value was based upon measured or nominal concentrations.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.